amino acid;

R^h is OH, NH_2, or $NHLysNH_2$;

each of R^i and R^j is, independently, a group selected from adamantoyl, alkyl, lipid, steroid, or an amino acid labeled with a fluorescent group; or R^i and R^j, together, are a group selected from adamantoyl, alkyl, lipid, or steroid; and

n is an integer from 1 to 30.

REMARKS

Claims 15-52 are pending in this application. Claims 15, 19, 21, 22, 23, 24, 25, 32, 39, and 46 have been amended. No claims have been added or deleted. The Office Action contains an objection to the specification and rejections under 35 U.S.C. §§§ 102, 103, and 112, first paragraph, which are discussed below.

The Office Action objects to the continuing application data as amended in the Reply filed November 2, 2000 as allegedly not providing the relationship between each application. Although Applicants respectfully disagree that no relationship is provided, certain further amendments have been made which Applicants believe render this objection moot.

Claims 15-17, 25, 26, and 31 stand rejected under 35 U.S.C. §102(b) as allegedly being unpatentable over the disclosure of Thomson et al., WO 93/12129 ("the Thomson reference"). This rejection has been maintained even in view of Applicant's acknowledged claim of priority because, according to the Office Action, the disclosure of "liphophilic functionality" in the Thomson reference is allegedly broader than that provided in Applicants' specification. Although Applicants respectfully disagree with this conclusion, the claims have been amended to

replace the term "lipophilic groups" in the definition of R^i and R^j with "groups selected from adamantyl, alkyl, lipid or steriod." With respect to alkyl, lipid and steroid groups, Applicants note that neither the present Office Action, nor any previous Office Action, has ever disputed that these groups are lipophilic species disclosed by Applicants' priority documents. Moreover, Applicants' priority document discloses the administration of PNA compounds into the cells of an organism (*see, e.g.*, column 7, lines 1-5). With respect to the group adamantyl, support for this amendment is provided, for example, in the originally filed figures that accompanied the application. It will be recognized that although adamantoyl groups are fully supported by the disclosure of "alkyl" in Applicants' earliest priority document at column 4, line 44, such compounds are neither taught nor suggested by the Thomson reference.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 102 based on the Thomson reference.

Claims 15-17, 25, 26, and 31 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious in view of the combined teachings of the Thomson reference and certain other references. These rejections, however, assume that the Thomson reference is available as prior art. Since this assumption is incorrect in view of the claims as amended, the rejections for alleged obviousness are believed to be overcome. Accordingly, Applicants respectfully request reconsideration and withdrawal of the art rejections under 35 U.S.C. §103.

Claims 23, 24, and 39-52 stand rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. Applicants respectfully request reconsideration of this rejection as

there is no reason to believe that one of ordinary skill in the art would not be able to practice the claimed methods and put them to their many uses.

Although the Office Action correctly states that claims are not enabled if, at the time the application was filed, undue experimentation would have been required to make and use the invention, the Office Action is clearly mistaken as to what is required to practice Applicants' claims. Particularly, the Office Action assumes that the specification must "enable the *therapeutic application* of the claimed invention." *See* Final Office Action mailed February 27, 2001, page 9 (emphasis added). What the present Office Action fails to recognize is that Applicants need not enable a therapeutic application of the claimed products or methods, or assure that they are optimized for clinical use. In fact, it is improper for the PTO to require any showing regarding the degree of effectiveness of therapeutic inventions, such as those now claimed. M.P.E.P. § 2107.02; *In re Sichert,* 566 F.2d 1154 (C.C.P.A. 1977).

The present Office Action criticizes Applicants for not producing any evidence to rebut the disclosures of Gewirtz, Rojanasakul, Hyrup, and Buchardt, which have been alleged to disclose "problems" associated with the therapeutic use of oligonucleotides. It is now undisputed, however, that these references nowhere suggest that those skilled in the art would not be able to practice the claimed invention to some measurable extent. Indeed, these articles are concerned exclusively with the feasibility of oligonucleotides as commercial products, and do not address uses of a non-commercial nature. Because there is no requirement in the patent laws that patentable inventions be commercially feasible, the conclusions drawn in these articles need

not be rebutted.

The Office Action also criticizes Applicants for not addressing additional factors enumerated in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988), such as the breadth of the claims at issue. Although Applicants believe that one of ordinary skill in the art would be able to practice the full scope of the claims as originally presented, Applicants note that certain amendments have been made to facilitate prosecution. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, in view of these amendments.

Applicants submit that the foregoing constitutes a full and complete response to the Office Action of record, and that claims 15-52 are in condition for ready allowance. An early Office Action to that effect is, therefore, earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

Respectfully submitted,

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Registration No. 44,154

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In The Specification:

The first full paragraph of page 1 has been amended as follows.

This patent application derives from International Patent Application PCT/US98/10804, filed on May 28, 1998, which claims priority to application Serial No. 08/864,765, filed on May 28, 1997 (now abandoned), which [claims priority to] is a continuation-in-part of application Serial No. 08/595,387, filed on February 1, 1996 (now U.S. Patent No. 5,773,571), which [claims priority to] is a continuation-in-part of Serial No. 08/054,363, filed on April 26, 1993 (now U.S. Patent No. 5,539,082).

In The Claims:

Claims 15, 19, 21, 22, 23, 24, 25, 32, 39, and 46 have been amended as follows.

15. A method of modulating cellular uptake and distribution of a peptide nucleic acid comprising the steps of:

(a) derivatizing a backbone position of said peptide nucleic acid; and

(b) conjugating the derivatized peptide nucleic acid of step (a) with a [lipophilic] group selected from adamantyl, alkyl, lipid, steroid or an amino acid labeled with a fluorescent group.

19. The method of claim 15 wherein said [lipophilic] group is an adamantyl group.

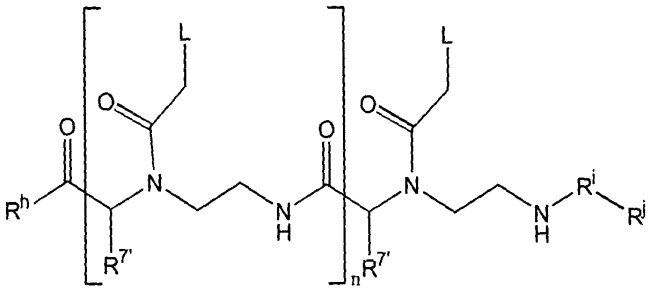
21. A method of modulating cellular uptake and distribution of a peptide nucleic acid comprising the steps of:

(a) conjugating said peptide nucleic acid with a [lipophilic] group selected from adamantyl, alkyl, lipid, steroid or an amino acid labeled with a fluorescent group; and

(b) introducing the conjugated peptide nucleic acid of step (a) into liposomes.

22. The method of claim 21 wherein said [lipophilic] group is an adamantyl group.

23. A pharmaceutical composition comprising [the peptide nucleic acid according to claim 1] a peptide nucleic acid having formula:



wherein:

each L is, independently, a naturally-occurring nucleobase or a non-naturally-occurring nucleobase;

each $R^{7'}$ is hydrogen or the side chain of a naturally-occurring or non-naturally-occurring

amino acid, at least one $R^{7'}$ being the side chain of a naturally-occurring or non-naturally-occurring amino acid;

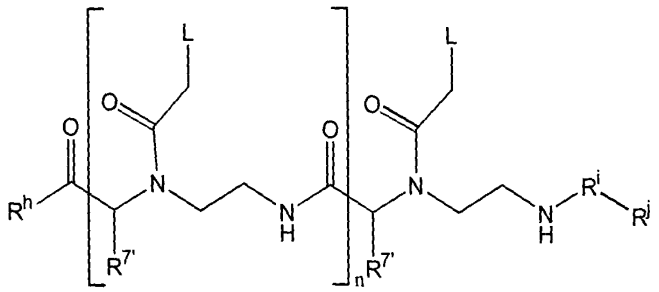
R^h is OH, NH_2, or $NHLysNH_2$;

each of R^i and R^j is, independently, a group selected from adamantyl, alkyl, lipid, steroid or an amino acid labeled with a fluorescent group; or R^i and R^j, together, are a group selected from adamantyl, alkyl, lipid or steroid; and

n is an integer from 1 to 30;

and at least one pharmaceutically acceptable carrier, binder, thickener, diluent, buffer, preservative or surface active agent.

24. A pharmaceutical composition comprising [the composition of claim 8] a composition comprising a peptide nucleic acid incorporated into a liposome, said peptide nucleic acid having formula:



wherein:

each L is, independently, a naturally-occurring nucleobase or a non-naturally-occurring nucleobase;

each $R^{7'}$ is hydrogen or the side chain of a naturally-occurring or non-naturally-occurring amino acid;

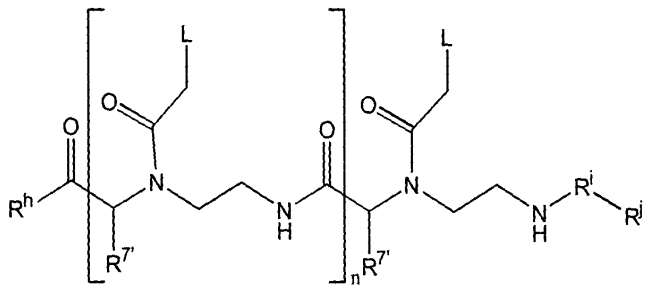
R^h is OH, NH_2, or $NHLysNH_2$;

each of R^i and R^j is, independently, a group selected from adamantyl, alkyl, lipid, steroid or an amino acid labeled with a fluorescent group; or R^i and R^j, together, are a group selected from adamantyl, alkyl, lipid or steroid; and

n is an integer from 1 to 30;

and at least one pharmaceutically acceptable carrier, binder, thickener, diluent, buffer, preservative or surface active agent.

25. A method of modulating cellular uptake and distribution of a peptide nucleic acid in a cell or tissue comprising administering to the cell or tissue a peptide nucleic acid having formula:



wherein:

each L is, independently, a naturally-occurring nucleobase or a non-naturally-occurring nucleobase;

each $R^{7'}$ is hydrogen or the side chain of a naturally-occurring or non-naturally-occurring amino acid, at least one $R^{7'}$ being the side chain of a naturally-occurring or non-naturally-occurring amino acid;

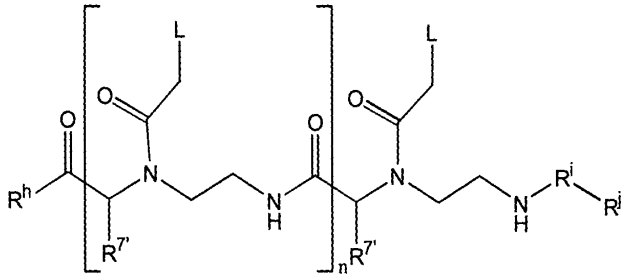
R^h is OH, NH_2, or $NHLysNH_2$;

each of R^i and R^j is, independently, a [lipophilic] group selected from adamantoyl, alkyl, lipid, steroid, or an amino acid labeled with a fluorescent group; or R^i and R^j, together, are a

[lipophilic] group selected from adamantoyl, alkyl, lipid, or steroid; and

n is an integer from 1 to 30.

32. A method of modulating cellular uptake and distribution of a peptide nucleic acid in a cell or tissue comprising administering to the cell or tissue a composition comprising a peptide nucleic acid incorporated into a liposome, said peptide nucleic acid having formula:



wherein:

each L is, independently, a naturally-occurring nucleobase or a non-naturally-occurring nucleobase;

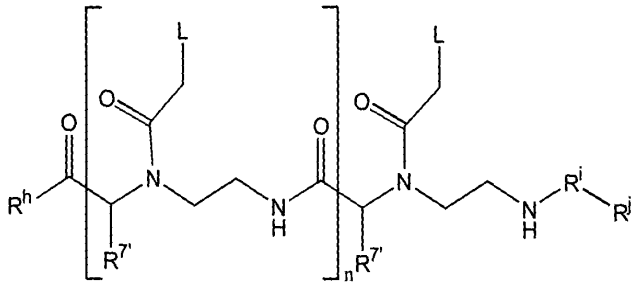
each $R^{7'}$ is hydrogen or the side chain of a naturally-occurring or non-naturally-occurring amino acid;

R^h is OH, NH_2, or $NHLysNH_2$;

each of R^i and R^j is, independently, a [lipophilic] group selected from adamantoyl, alkyl, lipid, steroid, or an amino acid labeled with a fluorescent group; or R^i and R^j, together, are a [lipophilic] group selected from adamantoyl, alkyl, lipid, or steroid; and

n is an integer from 1 to 30.

39. A method of treating an animal comprising administering to the animal a therapeutically effective amount of a peptide nucleic acid of formula:



wherein:

each L is, independently, a naturally-occurring nucleobase or a non-naturally-occurring nucleobase;

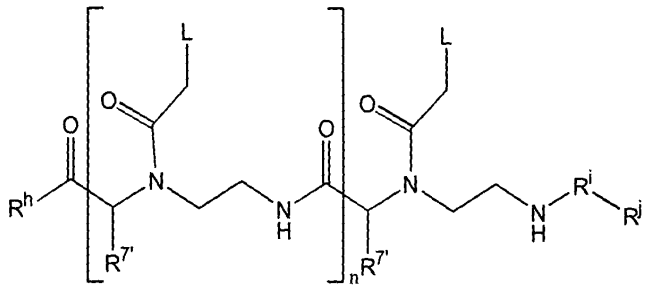
each $R^{7'}$ is hydrogen or the side chain of a naturally-occurring or non-naturally-occurring amino acid, at least one $R^{7'}$ being the side chain of a naturally-occurring or non-naturally-occurring amino acid;

R^h is OH, NH_2, or $NHLysNH_2$;

each of R^i and R^j is, independently, a [lipophilic] group selected from adamantoyl, alkyl, lipid, steroid, or an amino acid labeled with a fluorescent group; or R^i and R^j, together, are a [lipophilic] group selected from adamantoyl, alkyl, lipid, or steroid; and

n is an integer from 1 to 30.

46. A method of treating an animal comprising administering to the animal a therapeutically effective amount of a composition comprising a peptide nucleic acid incorporated into a liposome, said peptide nucleic acid having formula:



wherein:

each L is, independently, a naturally-occurring nucleobase or a non-naturally-occurring nucleobase;

each $R^{7'}$ is hydrogen or the side chain of a naturally-occurring or non-naturally-occurring amino acid;

R^h is OH, NH_2, or $NHLysNH_2$;

each of R^i and R^j is, independently, a [lipophilic] group selected from adamantoyl, alkyl, lipid, steroid, or an amino acid labeled with a fluorescent group; or R^i and R^j, together, are a [lipophilic] group selected from adamantoyl, alkyl, lipid, or steroid; and

n is an integer from 1 to 30.